Safety Data Sheet

Demecolcine

Division of Safety
National Institutes
of Health

WARNING!

THIS COMPOUND IS ACUTELY TOXIC, TERATOGENIC, AND EMBRYOTOXIC. IT IS READILY ABSORBED THROUGH THE INTESTINAL TRACT AND TRANSPLACENTALLY. IT MAY CAUSE SEVERE IRRITATION OF MUCOUS MEMBRANES. AVOID FORMATION AND BREATHING OF AEROSOLS.

LABORATORY OPERATIONS SHOULD BE CONDUCTED IN A FUME HOOD, GLOVE BOX, OR VENTILATED CABINET.

AVOID SKIN CONTACT: IF EXPOSED, WASH WITH SOAP AND COLD WATER. AVOID WASHING WITH SOLVENTS AND EXPOSURE TO UV LIGHT. AVOID RUBBING OF SKIN OR INCREASING ITS TEMPERATURE.

FOR EYE EXPOSURE, IRRIGATE IMMEDIATELY WITH LARGE AMOUNTS OF WATER. FOR INGESTION, INDUCE VOMITING. DRINK MILK OR WATER. REFER FOR GASTRIC LAVAGE. FOR INHALATION, REMOVE VICTIM PROMPTLY TO CLEAN AIR. ADMINISTER RESCUE BREATHING IF NECESSARY. REFER TO PHYSICIAN.

IN CASE OF LABORATORY SPILL, WEAR PROTECTIVE CLOTHING DURING CLEANUP. AVOID SKIN CONTACT OR BREATHING OF AEROSOLS. USE ETHANOL OR ACIDIFIED WATER TO DISSOLVE COMPOUND. USE ABSORBENT PAPER TO MOP UP SPILL. DISPOSE OF WASTE SOLUTIONS AND MATERIALS APPROPRIATELY.

A. Background

Demecolcine (DMC) is a medicinally active alkaloid of Colchicum autumnale L., Liliaceae (autumn crocus, meadow saffron) as well as of other species of the Liliaceae family. It is a pale yellow crystalline compound, soluble in acidified water, ethanol, ether, chloroform, and benzene and, like the closely related colchicine,

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sensitive to UV light. Also like colchicine it is a strong antimitotic agent; its chief toxic action is due to a specific binding to tubulin, the subunit protein of microtubules which are structures found in all eukaryotic cells where they participate in mitosis, cell shaping, secretion, motility, and other functions. This binding results in inhibition of tubulin polymerization and therefore of mitosis in the anaphase of the normal mitotic cycle. DMC has been used as an antineoplastic and in the treatment of gou

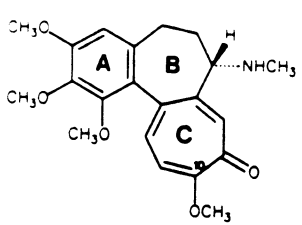
There are no specific reviews of DMC, but its chemical and biological properties closely resemble those of colchicine. Short mention of these properties is made by Creasey (1975).

B. Chemical and Physical Data

1. Chemical Abstract Nos.: 477-30-5 for the biologically active (S) form; 102491-77-0 for the racemic form.

2. Synonyms: 6,7-Dihydro-1,2,3,10-tetramethoxy-7-(methylamino)-benzo(α)heptalen-9(5H)-one; benzo[α]heptalen-9[5H]-one, 6,7 dihydro-1,2,3,10-tetramethoxy-7-(methylamino)-,(S)-;[A] Colchicine, N-deacetyl-N-methyl;[B] Colcemid(e); Colchamine; Desmecolchine; NSC 3096; Omain(e); Santavy's Substance F; Alkaloid HB.

3. Chemical Structure and molecular weight:



$C_{21}H_{25}NO_5$; 371.42

4. Density: No data.

5. Optical rotation: $[\alpha]_D^{20}$ = -123.5 in chloroform (Capraro and Brossi, 1979).

[A]Chemical Abstracts name, used for listings in 9th Decennial Index and subsequently.

[B]Chemical Abstracts name, used for listings in 7th and 8th Decennial Index.

6. Absorption spectroscopy: Ultraviolet absorption maxima in ethanol at 245 (log ε = 4.55) and 355 nm (log ε = 4.24). Infrared, NMR, and mass spectral data have been published (Capraro and Brossi, 1979). Free DMC exhibits little or no fluorescence but has marked fluorescence when bound to tubulir (Bhattacharyya and Wolff, 1974).

7. Volatility: No data; may be regarded as essentially non-volatile.

8. Solubility: No quantitative data. DMC is stated to be "solub in acidified water, in alcohol, ether, chloroform, benzene" (Windholz, 1983).

9. Description: Pale yellow prisms when crystallized from ethyl acetate/ether.

0. Boiling point: No data; melting point: 186°C.

1. Stability: Little published information; by analogy with colchicine it may be assumed that DMC in aqueous solution shou be quite heat stable when protected from sunlight. DMC darken on exposure to UV light and it has been stated that photoreac-tion products are formed which are analogous to the lumicol-chicines produced from colchicine on such exposure (Hart and Sabnis, 1976). The structures of these lumicolchicines have been depicted (Wyatt et al., 1981). These photodegradation products are physiologically inactive, and care must be taken storage and analysis of DMC to prevent exposure to sunlight. Ethanol solutions of colchicine, kept in amber bottles, may be stored at -15°C and the same probably is true also for DMC.

. Chemical reactivity: No data. One may assume, in analogy with colchicine, that demethylation of the methoxy group at C_{10} occurs in dilute acid, and that permanganate oxidation destroys the B and C rings and results in trimethoxyphthalic acid.

. Flash point: No data.

. Autoignition temperature: No data.

. Explosive limits in air: No data.

ire, Explosion, and Reactivity Hazard Data

. DMC does not require special fire-fighting procedures or equipment and does not present unusual fire and explosion hazards.

. Acid, alkali, and oxidants contribute to the instability of DMC

3. DMC is highly sensitive to exposure to visible or ultraviolet light. No other incompatibilities are known.

4. DMC does not require non-spark equipment.

Operational Procedures

The NIH Guidelines for the Laboratory Use of Chemical Carcinogens describe operational practices to be followed when potentially carcinogenic chemicals are used in NIH laboratories. The NIH Guidelines should be consulted to identify the proper use conditio required and specific controls to be implemented during normal and complex operations or manipulations involving DMC.

It should be emphasized that this data sheet and the NIH Guideline are intended as starting points for the implementation of good laboratory practices when using this compound. The practices and procedures described in the following sections pertain to the National Institutes of Health and may not be universally applicabl to other institutions. Administrators and/or researchers at other institutions should modify the following ite as needed to reflec their individual management system and current occupational and environmental regulations.

1. Chemical inactivation: No validated method reported.

2. Decontamination: Turn off equipment that could be affected by DMC or the materials used for cleanup. If there is any uncertainty regarding the procedures to be followed for decontamination, call the NIH Fire Department (dial 116) for assistance. Use absorbent paper to mop up spill. Wipe off surfaces with ethanol or acidified water, then wash with copiou quantities of water. Glassware should be rinsed in a hood with ethanol or acidified water, followed by soap and water. Animal cages should be washed with water.

3. Disposal: No waste streams containing DMC shall be disposed of in sinks or general refuse. Surplus DMC or chemical waste streams contaminated with DMC shall be handled as hazardous chemical waste and disposed of in accordance with the NIH chemical waste disposal system. Nonchemical waste (e.g., anima carcasses and bedding) containing DMC shall be handled and packaged for incineration in accordance with the NIH medical-pathological waste disposal system. Potentially infectious waste (e.g., tissue cultures) containing DMC shall be disinfected by heat using a standard autoclave treatment and package for incineration, as above. Burnable waste (e.g., absorbent bench top liners) minimally contaminated with DMC shall be handled as potentially infectious waste and packaged for incineration, as above. Absorbent materials (e.g., associated with spill cleanup) grossly contaminated shall be handled in accordance with the chemical waste disposal system. Radioactiv waste containing DMC shall be handled in accordance with the NI radioactive waste disposal system.

4. Storage: Store solid DMC and its solutions in dark-colored, tightly closed containers under refrigeration. Avoid exposure to light and moisture. Store working quantities of DMC and its solutions below -10°C in amber bottles with caps and Teflon cap liners.

Monitoring and Measurement Procedures Including Direct Field Measurements and Sampling for Subsequent Laboratory Analysis

1. Sampling: For any analytical procedure, care must be taken to avoid exposure to sunlight or ultraviolet light. Urine collections, extractions, centrifugations, etc. should be carried out in glassware wrapped in aluminum foil or in amber bottles. It is preferable to carry out these operations at low temperatures and as rapidly as possible.

2. Analysis: No specific method has been described. Methods for separation of DMC and its possible metabolites by high performance liquid chromatography have been investigated (Davis and Klein, 1980; Klein and Davis, 1981). Analytical procedures originally developed for colchicine, using HPLC (Wyatt et al., 1981), radioimmunoassay (Schermann et al., 1980), or fluorimetry (Bourdon and Galliot, 1976) can probably be adapted for use with DMC.

Biological Effects (Animal and Human)

1. Absorption: DMC is absorbed from the gastrointestinal tract and presumably, because of its teratogenic effects, transplacentally.

2. Distribution and pharmacokinetics: No data.

3. Metabolism and excretion: No data.

4. Toxic effects: There are very few data on the acute LD50 of DMC but those that do exist afford an interesting comparison with the toxicity of colchicine. The intravenous LD50 in the rat (1.70 mg/kg: Scherf et al., 1970) is about the same as for colchicine (1.6 mg/kg: Rosenbloom and Ferguson, 1968); but the intramuscular LD50 in the mouse is 88 mg/kg as compared with 1.2 mg/kg for colchicine (Rösner et al., 1981), and the mouse intraperitoneal LD50 of DMC and colchicine is 35 and 3.5 mg/kg, respectively (Quinn and Milne, 1986; Fleischmann et al., 1962). From these few data one may conclude that DMC, by routes other than the intravenous, is considerably less toxic than colchicine. There is no information on which to judge whether the considerable species variation in toxicity found for colchicine is found for DMC also.

   The principal toxic action of DMC appears to be its reaction with tubulin, a dimer of two proteins of molecular weight 55,000

each. This binding results in prevention of assembly of microtubules. Compared with the similar reaction of tubulin with colchicine, the rate of binding is higher for DMC but this binding is reversible while that of colchicine is almost irreversible (Ray et al., 1981; Bhattacharyya et al., 1986); obviously the bulk and/or type of substituent on the B ring has a bearing on this reaction.

Effects on intraocular pressure by both compounds have been noted but while colchicine has strong effects after both topical and intravitreal application, DMC exerts this effect only on intravitreal injection (Williams and Bhattacherjee, 1982).

There are no data on toxic symptoms in man during clinical use of DMC but these may be similar to those described for colchicine (Arena and Drew, 1986) which consist of severe abdominal pain, vomiting, diarrhea, and renal symptoms.

5. Carcinogenic effects: No carcinogenic effects due to DMC have been noted (Schmähl, 1969, 1975). DMC has been mentioned as being an antineoplastic (Windholz, 1983) but there are no literature references to its actual use in this role.

6. Mutagenic and teratogenic effects: Mutagenic effects of DMC have not been described. However, DMC is highly embryotoxic in rabbits though not in monkeys (Morris et al., 1967) and teratogenic in rats (Thiersch, 1958). Treatment of two pregnant leukemic patients with DMC resulted in no fetal abnormalities (Sokal and Lessmann, 1960).

Emergency Treatment

1. Skin and eye exposure: For skin exposure, remove contaminated clothing and wash skin with soap and water. Skin should not be rinsed with organic solvents or scanned with UV light. Avoid rubbing of skin or increasing its temperature. For eye exposure, irrigate immediately with copious quantities of running water for at least 15 minutes. Obtain ophthalmological evaluation.

2. Ingestion: Drink plenty of water or milk. Administer activated charcoal. Induce vomiting. Refer for gastric lavage.

3. Inhalation: Remove victim promptly to clean air. Administer rescue breathing if necessary.

4. Refer to physician at once. Consider treatment for pulmonary irritation, shock, and/or abdominal pain.

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